EDITORIAL

Slow Virus Diseases

THE REVIEW BY DR. ADAMS elsewhere in this issue on the subject of persistent or slow virus diseases deals with a very broad subject of great current importance, particularly in regard to today's most significant health problems such as many of the chronic diseases including cancer, mental disabilities and even the process of aging itself.

A few points made by Dr. Adams—or ones that are derivative from his paper—will be highlighted and are selected solely on the basis of the prejudices of the writer of this editorial.

Dr. Adams appropriately emphasizes the critical role that the careful study of animal models such as scrapie of sheep, lymphocytic choriomeningitis of mice and malignancies of fowl has played in the development of our understanding of these diseases. However, it should be recognized that the tremendous progress in our understanding of the molecular biology of cell-virus interactions and genetics, much of which has evolved from the seminal studies with bacteriophage, has opened up new ways of thinking about virus diseases and provided a framework for constructing testable hypotheses that have been of particular value in cancer but are potentially more widely applicable to many of the chronic diseases. For example, the recognition that the genome of the bacteriophage could persist in infected bacteria and their progeny, only forming complete virus when provoked by various stimuli (Lysogeny), has been found to have possible counterparts in animals and man such as recurrent herpes simplex, herpes zoster, subacute sclerosing panencephalitis and the like. However, the discovery that virus infection could result in new inherited attributes of the host cell has had a profound influence upon the approach of investigators to the study of mammalian viruses that so far has proved particularly fruitful in regard to cancer.

The long interval between initiation of infection and the appearance of disease that characterizes slow, persistent infections has important implications for human disease but presents a very difficult problem in diagnosis.

It must be emphasized that slow and persistent virus infections are associated with two classes of agents: the conventional viruses that meet the usual morphologic and biochemical criteria and the unconventional agents that lack many features usually exhibited by viruses (indeed, one wonders whether they truly qualify as viruses).

The diseases that the latter agents are known to cause are scrapie of sheep, mink encephalopathy, and Kuru and Creutzfeldt-Jakob disease in man. They are all characterized by very long incubation periods, a slow but relentless course and symptoms and pathologic findings limited to the central nervous system—the latter characterized by neuron loss and vacuolization but with no evidence of inflammation. No antibodies against these agents have been noted nor has anything resembling a virion or specific structure been identified. They are unusually resistant to physical agents and nucleases. All in all, they present a fascinating and difficult problem, not too different from that once presented by conventional viruses when all that was known about them was that they replicated, caused disease and passed through filters that retained bacteria. The one outstanding difference that will make the unconventional viruses more difficult to study is the lack of antibodies to them. Thus, it is not possible to separate strains or detect their presence without animal inoculation. New ideas and approaches will be needed if we are to understand these curious agents and delineate their true importance in nature.

Recently a group of agents called viroids that cause diseases of plants has been described.[1] Viroids have some attributes in common with the

unconventional slow viruses in that they appear to lack any structural protein but consist only of naked ribonucleic acid (RNA). Studies of these agents may prove useful to our understanding of their animal counterparts.

An interesting and important matter to recognize is the extraordinary differences that are seen in the diseases produced by a single virus. Who would have anticipated that such an ordinary run-of-the-mill virus such as measles would be found to cause not only the acute illness of classical measles but a highly fatal indolent encephalitis (SSPE) from 1 to 20 or more years after the acute infection and to be a prime suspect as an etiologic agent of a chronic relapsing central nervous system disease—multiple sclerosis?

It is quite apparent that the simplistic view of a virus disease or infection as an acute self-limiting episode followed by immunity and elimination of the virus can no longer be sustained. It seems probable that persistence of virus in some form in some cells of the body is the more usual outcome, dependent to a considerable degree upon the age of the host at the time of infection and other factors relating to the immunologic capacity of the host and genetic characteristics of the virus. Persistent infection may be harmless or may cause disease by a variety of mechanisms. These include slowly progressive cell destruction and immune disease as the result of deposition of antibody-virus complexes or in response to cells antigenically altered by virus or by the activation of latent virus by a variety of mechanisms—which include alteration of immune responsiveness due to disease, aging or immunosuppressive therapy.

Speculation concerning the role of viruses in a variety of disease states can easily sound like science fiction. However, on the basis of what we now know of viral replication and the intimate relationship between viral nucleic acids and the genetic apparatus of the cell, extraordinary possibilities become hypothetically feasible. Therefore, it would seem most likely that it is only a matter of time until at least some human cancers are proven to be caused by viruses. An etiologic role of viruses, particularly measles, in multiple sclerosis is highly probable. Animal models exist that implicate viruses in conditions that resemble multiple myeloma and various of the so-called autoimmune diseases and, as already pointed out, theoretical grounds also exist to support such an hypothesis. Gajdusek[2] has stated that the pathology of the spongioform encephalopathies may resemble the process of normal aging and has raised the question as to whether or not viruses may accelerate the rate of aging.

Far out ideas? Perhaps, and certainly not easy to prove, but with viruses it is hard to conceive of anything as completely impossible. However, keep in mind that it is a virologist speaking.

FREDERICK C. ROBBINS, MD
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REFERENCES

1. Marx JL: "Viroids"—A new kind of pathogen? Science 178: 734, Nov 17, 1972
2. Gajdusek DC: Slow virus infection and activation of latent infections in aging, *In* Strekler B (Ed): Advances in Gerontological Research, Vol 4. New York, Academic Press, 1972, pp 201-218

The Fluoridation of Drinking Water

THE FLUORIDATION of drinking water continues to be a public health issue in many places in the United States. It has been and remains the subject of scientific, social, economic and political scrutiny by both its advocates and its opponents. The subject is examined further elsewhere in this issue of THE WESTERN JOURNAL OF MEDICINE, this time in relationship to dietary fluoride ingestion.

It is perhaps worth noting that as recently as last December the House of Delegates of the American Medical Association adopted upon recommendation of its Council on Foods and Nutrition[1] a statement on fluoridation which includes the following significant comment:

"No alternative techniques for the prophylactic application of fluorides can at present replace the fluoridation of drinking water as an effective and practical public health measure. Where water fluoridation at optimal levels cannot be used, however, other ways of supplying the proper amount of fluoride should be encouraged."

Until there is convincing evidence to the contrary we believe the fluoridation of drinking water is a desirable public health measure and that it should continue to be supported by the medical profession.

REFERENCE

1. Fletcher DC: Revised statement on fluoridation—AMA Council on Foods and Nutrition (Adopted Dec 1, 1974, by AMA House of Delegates) (Editorial). JAMA 231:1167, Mar 17, 1975